## REMARKS

Claims 25, 26, 30, 74, 76-80, 83-84, 87-88, 105-106, 110, 112-117, 122-129, and 131-134 are pending and subject to examination.

Amendment to Claim 30

Claim 30 is currently amended. Claim 30 refers to "a recombinant anti-integrin antibody, or an antigen binding fragment thereof, which specifically binds to the open conformer of an αL integrin I-domain relative to the closed conformer of an αL integrin I-domain." Support for the amendment can be found throughout the specification. As an initial matter, "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." MPEP 2163.02. The Applicants have merely used clearer and more explicit language to describe some of the antibodies mentioned in the specification, e.g., at page 12, lines 27-31

> anti-integrin antibodies which specifically recognize a modified integrin I-domain polypeptide, e.g., an anti-LFA-1 antibody which specifically recognizes a modified LFA-1 I-domain polypeptide, that are selective for a **particular** conformer, e.g., **an open conformer** or a closed conformer,

This passage, alone and in combination with other passages in the text, clearly describes the concept of an antibody which specifically binds to one conformer relative to another. Indeed, the above passage cannot be construed to refer to an antibody that binds to both open and closed LFA-I domain relative to some completely unrelated protein (such as BSA). Clearly, if Applicants were referring to such an antibody, Applicants would not have invoked the terms "selective" and "a particular conformer." The only natural reading of the above passage is that the described antibody binds to one particular conformer relative to the other.

This interpretation is also compelled by other passages in the specification. For example, at page 4, lines 17-14, Applicants preface the invention with the following statement:

> In addition to integrins, many pharmaceutically important proteins exist in two alternative three-dimensional structures, referred to as conformations or conformers. Often these proteins have important signaling functions, such as

> small G proteins, trimeric G protein a subunits, tyrosine kinases, and G protein-coupled receptors. Typically, one of these conformations and **not** the other is enzymatically active or has effector functions. Therefore, **antibody** or small molecule therapeutics that are **specific for a protein in a particular conformation, for example, the active conformation, would have great advantages over non-selective alternatives**.

In this context, "non-selective alternatives" refers to antibodies that bind to the protein, but are not specific for a particular alternatives. Having disavowed such non-selective antibodies, the Applicants introduce the invention, at page 4, lines 29-30, as including:

> antibodies, e.g., anti-LFA-1 antibodies . . . that are specific for a desired protein conformation, e.g., an "open" or active conformation or a "closed" or inactive conformation . . .

The specification is replete with further discussion of antibodies that "selectively bind to an integrin I-domain polypeptide in the open conformation, an integrin I-domain polypeptide in the closed conformation, or a modified integrin I-domain polypeptide." Specification, e.g., at page 6, lines 17-19. Given that one principal aspect of the specification is the discover of modified I-domains locked in a particular conformation, these statements cannot be construed as references to an antibody that binds to an I-domain independent of its conformation, i.e., mere I-domain binding antibodies.

Rejections for Alleged Lack of Enablement

The Examiner rejected claims 25-27,29-30,73-80,83-88, 102, 103, and 105-130 for lack of enablement. The Applicants respectfully disagree with the substance of the Examiner's rejection. Note that the Applicants have amended the independent claims 26, 84, 131 and 132 to recite language that more closely corresponds to the material that the Examiner deemed enabled. In particular, the Examiner noted that the specification is:

> **enabling for an antibody or an antigen binding fragment thereof, which specifically binds to a modified integrin I-Domain in the open conformation comprises substitutions E284/E301C or K287CK294C in an aL subunit but not to a modified integrin I-domain in the closed conformation by the substitutions of K289CK294C**

With respect to claims that refer to pharmaceutical compositions (127-130), the Examiner further asserted that:

> **Also, at issue is whether or not the claimed composition recited in claims 127-130 would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant 's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.**

Claims 117-124 were similarly rejected. The Examiner's enablement rejections of claims to pharmaceutical compositions and antibodies linked to therapeutic moieties are based only on conclusory assertions. The Applicants respectfully that the Examiner has not satisfied his burden under MPEP § 2164.04, which states in relevant part that:

> [T]he examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. . . [T]he minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments. . . . **The language should focus** on those factors, reasons, and **evidence** that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims.

The Applicants refer the Examiner, e.g., to pages 41-49 of the specification, which describes making and using the claimed pharmaceutical compositions and therapeutics. In addition, those skilled in the art were aware of disclosures, such as that of U.S. 5,622,700 which teaches therapeutic methods for using a conventional anti-LFA-1 antibody.

With respect to claims not limited to particular substitutions, the Examiner argued in part:

> **It is not clear how one of skill would make an antibody to any integrin in the open conformation . . . other than an antibody directed to the specific open conformation mutations E284/E301C or K287/K294C in the αL subunit I-domain and tested . . . with the specific closed conformation mutation K289C/K294C in the αL subunit I-domain to indicate that the resultant antibody does not bind to**

**the closed conformation. Without some kind of substantive structure of an I-domain in the open conformation, it would require undue experimentation for one of skill to make antibodies to that would bind to the open conformation but not to the closed conformation encompassed by the instant claims.**

The specification does teach how to make an integrin in the open conformation and provides a number of example of modification of integrins in the open conformation. For example, page 15, lines 27-30 of the specification teach a number of αL mutations that are stabilized in the open conformation ("K287C/K294C, E284C/E301C, L161C/F299C, K160C/F299C, L161C/T300C, and L289C/K294C mutants"). Moreover, Example 1 of the specification at pages 56-59 teaches an exemplary method for designing mutant αL I-domain or other I-domains in the open conformation.

In addition, the specification does teach a substantive structure for an I-domain in the open conformation. See, for example, page 56, lines 10-12 and the accompanying disclosure which teaches using the open conformation structure of the Mac-1 I domain (1ido) from Lee et al., *Structure* 3:1333 (1995) and to use this structure to model the open conformation of other I-domains. Thus, contrary to the Examiner's assertion, the application does teach substantive structures of I-domains in the open conformation.

Accordingly, the Applicants respectfully submit that there is no basis for the rejections for lack of enablement and request that the rejection be withdrawn.

Claim Construction of the Term "*Specifically Binds*"

Before turning to the art rejections applied against claim 25 and claims dependent therefrom, it is necessarily to resolve the proper construction of the term "specifically binds." The Examiner stated the following view:

**Regarding the antibodies that bind "equally well " to both the open and closed conformation, Applicant declared that these antibodies are not antibodies that "specifically bind " to a n integrin I-domain in the open conformation. Applicant submits that the disclosed monoclonal antibodies referred to by the Examiner are not examples of the claimed antibodies.**

**However, Applicant 's argument attempts to limit the term "specifically bind " in a manner inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequences.**

**That is an antibody "cross-reacts ", i. e., binds to more than one protein sequence, does not mean that the antibody does not "specifically react " with both proteins.**

The issue before us is whether "specific binding," as used in this application, is relative to some remote protein not mentioned in the specification (such as serum albumin) or relative to an integrin in a different conformation.

Indeed, in any circumstance, the term "specific binding" is relative. For example, specific binding of an antibody to an HIV-1 coat protein might mean that the antibody can distinguish a viral HIV protein from a human cellular protein (say actin), or that the antibody can distinguish between an HIV protein and a herpes virus protein, or that the antibody can distinguish an HIV-1 protein from an HIV-2 protein. All these interpretations are consistent with the art known meaning of the term "specific binding." As the art known meaning is insufficient to resolve the matter, it is merely a point for departure. Context is required to resolve the appropriate meaning.

The Examiner relies on his view of the art-known definition of the term "specifically binds." The Applicants do not accept the Examiner's definition and respectfully submit that the Examiner did not give sufficient weight to the specification in construing the term.

The recent case AstraZeneca AB v. Mutual Pharmaceutical Co., Inc., held that a clear lexicography or disavowal in the specification operate to limit art-known definitions.[1] 384 F.3d 1333 (Fed. Cir. 2004) The Federal Circuit began by observing:

> A long line of cases indicates that evidence intrinsic to the patent -- particularly the patent's specification, including **the inventors' statutorily-required written description of the invention -- is the primary source for determining claim meaning**.

Slip Opinion at 5.

The Court acknowledges the importance of a term's ordinary meaning, but notes that, nevertheless, the intrinsic evidence can overcome the ordinary meaning by providing a "clear lexicography" or a "disavowal." Slip Opinion at 9-10. The Court went on to find that a "clear lexicography" does not require an explicit statement:

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[1] Applicants do not accede that the Examiner's characterization of art-known definitions.

> [The patentees] seems to suggest that lexicography requires a statement in the form "I define ____ to mean ____," but such rigid formalism is not required. See, e.g., Bell Atl. Network Servs., Inc., 262 F.3d at 1268 ("[A] claim term may be clearly redefined without an explicit statement of redefinition. . . . [T]he specification may define claim terms 'by implication' such that the meaning may be 'found in or ascertained by a reading of the patent documents.'" (citation omitted)).

In this application, the Applicants have clearly and repeatedly use the term "selective binding" or "specific binding" to refer to binding to one particular conformation, i.e., one conformation rather than another. The Applicants again refer the Examiner to the passages also quoted above on pages 8-9 of this response and repeated below. At page 12, lines 27-31:

> anti-integrin antibodies which specifically recognize a modified integrin I-domain polypeptide, e.g., an anti-LFA-1 antibody which specifically recognizes a modified LFA-1 I-domain polypeptide, that are selective for a **particular** conformer, e.g., **an open conformer** or a closed conformer,

At page 4, lines 17-14:

> Typically, one of these conformations and **not** the other is enzymatically active or has effector functions. Therefore, **antibody** or small molecule therapeutics that are **specific for a protein in a particular conformation, for example, the active conformation, would have great advantages over non-selective alternatives**.

The usage of the terms "specific binding" and "selective binding" throughout the specification provide a clear lexicography which defines these terms to mean specificity for one conformer relative to another. Moreover, as discussed in the Applicant's Reply dated June 2, 2004, the usage of these terms in the specification requires a degree of preference that is more pronounced than the negligible preferences of antibodies that are described in the specification as binding "equally well" to open and closed conformation I-domains.

In fact, the specification indicates that a difference in the range of 0%-18% for binding to the open versus the closed conformation I-domains does not amount to specific binding, whereas a difference of about 50% or greater does amount to specific binding. At page 63, lines 8-10 of the specification, the Applicants defined the differences observed in Table 2 of the specification as "equal" and therefore, not as "specifically" binding:

> All of the antibodies, except for CBRLFA-1/1, bound to the mutants K287C/K294C and L289C/K294C and wild-type LFA-1 equally well (Table 2), indicating that the cysteine substitutions did not disrupt the I-domain structure. Binding of monoclonal antibody CBRLFA-1/1 to the high-affinity open mutant K287C/K294C was reduced to 40-50% of wild-type, however, this antibody reacted with mutant L289C/K294C and the single cysteine substitution mutants K287C, L289C and K294C as well as wild-type.

Thus, as Applicants have used the terms, all the antibodies (except CBRLFA-1/1) in Table 2 of the specification bind "equally well" to mutants K287C/K294C and L289C/K294C. The table below recapitulates Table 2 of the specification but also expresses this data as a percentage difference in columns numbered #2 and #3. As shown in columns #2 and #3, the percentage differences in binding among these antibodies range, in absolute value, between 0-18%:

| | | | K287/K294C | | L289C/K294C | |
|---|---|---|---|---|---|---|
| | Col. #2 | Col. #3 | | | | |
| **ANTIBODY** | %-293T | *%K562T* | 293T | K562 | 293T | K562 |
| BL5 | **7%** | **-6%** | 92 | 92 | 86 | 98 |
| F8.8 | **12%** | **9%** | 94 | 102 | 84 | 94 |
| TS2/6 | **8%** | **-7%** | 85 | 89 | 79 | 96 |
| May.035 | **13%** | **-8%** | 93 | 93 | 82 | 101 |
| TS1/11 | **0%** | **-9%** | 94 | 96 | 94 | 105 |
| TS1/12 | **-13%** | **-18%** | 89 | 87 | 102 | 106 |
| TS1/22 | **5%** | **-15%** | 96 | 93 | 91 | 110 |
| TS2/14 | **4%** | **-8%** | 86 | 95 | 83 | 103 |
| 25.3.1 | **2%** | **2%** | 93 | 88 | 91 | 86 |
| *CBR LFA-1/1* | ***-54%*** | ***-53%*** | *44* | *56* | *96* | *118* |
| S6F1 | **-6%** | **13%** | 89 | 97 | 95 | 86 |
| TS1/18 | **4%** | **-8%** | 100 | 97 | 96 | 106 |
| YFC51 | **8%** | **-9%** | 103 | 101 | 95 | 111 |
| CLBLFA-1/1 | **ND** | **-5%** | ND | 96 | ND | 101 |
| May.017 | **ND** | **-2%** | ND | 109 | ND | 111 |
| 6.5e | **ND** | **-13%** | ND | 84 | ND | 96 |
| CBR LFA-1/7 | **3%** | **-2%** | 95 | 95 | 92 | 97 |
| CBR LFA-1/2 | **ND** | **0%** | ND | 86 | ND | 86 |
| YTA-1 | **ND** | **3%** | ND | 111 | ND | 108 |

Column 2 was calculated as (column#4/column#6 – 1).
Column 3 was calculated as (column#5/column#7 – 1).
Columns 4-7 were obtained from Lu et al.

Accordingly, a difference in the range of 0%-18% is, by definition, binding "equally well" to the open conformation and the closed conformation. Binding "equally well" to the open and closed conformations cannot amount to specifically binding to the open conformation.

The one exception, CBRLFA-1/1 is also illustrative. The Applicants noted at page 63, line 8, the CBRLFA-1/1 antibody does not bind "equally well," but appears to bind better to an I-domain in the closed conformation. Binding to the open conformation is reduced about 50% (see table above). Since the about 50% deviation by CBRLFA-1/1 is greater than 0%-18% range of values considered as binding "equally well," it follows that the Applicants excepted CBRLFA-1/1 from the category of antibodies that do not show specificity.

Thus, when the specification as a whole is considered in view of the current Federal Circuit law on claim construction and the factors mentioned above, among others, the Applicants clearly set forth a description of antibodies that specifically bind to the open confomer of an I-domain that requires experimentally significant degree of preferential binding to the open conformation relative to the closed conformation.

Rejection of Claims 25-27, 29-30, 73-80 and 82 under § 103

The Examiner has maintained the rejection of claims 25-27, 29-30, 73-80 and 82 in view of Huang and Lu. The rejection is respectfully traversed.

The antibodies described in Huang do not "specifically bind" to the open conformation, as Applicant's have used the term. The arguments presented in the Applicants' Reply dated June 2, 2004, are incorporated by reference herein. If the Examiner accepts the Applicant's construction of the claim term "specific binding," it is clear that the claimed antibodies do not have the binding properties of the antibodies described in Huang.

Rejection of Claim 26 under § 103

The Examiner has rejected claim 26 as obvious in view of Huang et al and various secondary references. The Examiner position appears to be that because the antibodies described in Huang et al. bind to a modified I-domain of αL that contains the K287C/K294C or

E284C/E301C mutations, they bind to an activation specific epitope. However, these antibodies, indisputable also bind to a modified I-domain that is locked in the closed conformation by the L289C/K294C mutation. See, e.g., Table 2 of Lu et al.

The Applicants have defined an activation specific epitope at at page 26, line 22 as "an epitope that is unique to an activated integrin." Thus, activation specific epitopes are absent from I-domains locked in the closed conformation. Antibodies that bind to an I-domain in the closed conformation necessarily do not bind to an activation specific epitope. Because the antibodies in Huang bind to a modified I-domain that is locked in the closed conformation, they do not bind to an activation specific epitope.

Summary: Claim 84

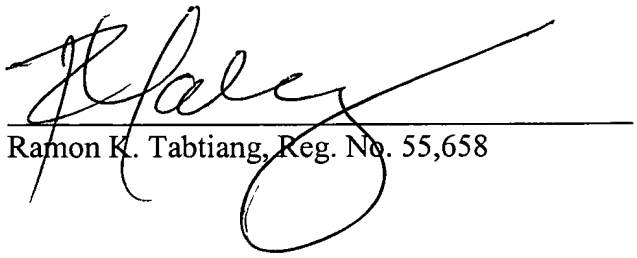
No art-based rejections have been made against claim 84 and claims dependent therefrom. The only rejection entered against claim 84 was alleged lack of enablement. This rejection is respectfully traversed above.

Conclusion

The Applicants respectfully submit that all claims are presently in condition for allowance, which action is respectfully requested. The Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do the Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

This response is being submitted with a Request for Continued Examination, an Information Disclosure Statement, and a Petition for Extension of Time. Please apply any other charges (including those required to maintain the pendency of this application, at any time) or credits to deposit account 06-1050, referencing attorney docket number 15775-029001.

Respectfully submitted,



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